REMARKS

I. Status of Claims:

Upon entry of the instant amendment, claims 15, 16, 19-22, 28-31, 36-39, and 44-83 will be pending in this application, claims 14, 17, 18, 23-27, 32-35, and 40-43 having been canceled herein, and claims 60-83 newly added. Claims 36-39 and 44-59 are presently withdrawn from consideration as drawn to a non-elected invention. All of new claims 60-83 belong in the presently elected group, along with pending claims 15, 16, 19-22, and 28-31.

Claims 15, 16, and 19-22 are rewritten in independent format and to make minor clerical changes. In addition, claims 20 and 22 are amended to specify 0-3 substitutions in the CDR sequences.

Support for the new claims and claim amendments can be found throughout the application as filed, *e.g.,* at page 5, line 28 to page 6, line 10; page 6, lines 18-33; and page 7, lines 3-12. No new matter has been added.

II. Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description:

Claims 17, 18, 20, and 22 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement (*see,* Office Action, pages 4-8).

Claims 17 and 18 have been canceled herein, so the rejection is moot as to those claims. Applicants address this rejection as it applies to claims 20 and 22, as amended, first noting for the record that the substance of this rejection appears to have been directed to the subject matter of claims 17 and 18, and not that of claims 20 and 22 .

Amended claim 20 recites: A diabody that recognizes CD22, wherein the diabody comprises (a) the amino acid sequences of CDRs 1-3 from SEQ ID NO:5 in which 0-3 amino acids in each of the CDRs of SEQ ID NO:5 are substituted with another amino acid; and (b) the amino acid sequences of CDRs 1-3 from SEQ ID NO:7 in which 0-3 amino acids in each of the CDRs of SEQ ID NO:7 are substituted with another amino acid; and wherein the diabody induces apoptosis of a tumor cell expressing CD22.

Amended claim 22 recites: A diabody that recognizes CD22, wherein the diabody comprises (a) the amino acid sequences of CDRs 1-3 from SEQ ID NO: 9 in which 0-3 amino acids in each of the CDRs of SEQ ID NO:9 are substituted with another amino acid; and (b) the amino acid sequences of CDRs 1-3 from SEQ ID NO:11 in which 0-3 amino acids in each of the CDRs of SEQ ID NO:11 are substituted with another amino acid; and wherein the diabody induces apoptosis of a tumor cell expressing CD22.

Applicants submit, as explained below, that a proper interpretation of the written description case law mandates a finding that Applicants' claims 20 and 22 (as amended) are in full compliance with the written description requirement under 35 U.S.C. § 112.

In *Capon v Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005), the Federal Circuit explained that the descriptive text needed to meet the written description requirement for generic claims depends on a variety of factors, such as the existing knowledge in the particular field, the extent and context of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter. *Capon* made clear that compliance with the written description requirement varies with the nature and scope of the invention at issue, and with the scientific and technological knowledge already in existence. Thus, there is no *per se* rule regarding what kind of disclosure is required for compliance with the written description requirement. This understanding of the written description requirement is reflected in *Invitrogen Corp. v. Clontech Lab. Inc.,* 429 F.3d 1052 (Fed. Cir. 2005). In *Invitrogen*, the patented invention at issue involved the genetic engineering of a functionally modified form of a protein, reverse transcriptase (RT). RTs are naturally-occurring enzymes which possess two distinct catalytic activities: the DNA polymerase and RNase H activities. Invitrogen scientists discovered that by deleting a section of the RT protein (using deletion mutagenesis) from a particular retrovirus they could make an RT variant that retains DNA polymerase activity, albeit with substantially reduced RNAse activity. Based on the disclosure of this single example of an RT variant derived from a specific strain of retrovirus and generated by a specific methodology, Invitrogen obtained a patent covering any RT variant possessing certain functional characteristics and derived from any retrovirus, yeast, Neurospora, Drosophila,

primate or rodent[1]. Clontech argued that the claims violated the written description requirement in that the claims described the variant RTs in essentially functional terms, with no specific structural limitation. The Federal Circuit acknowledged that the claimed genus of variant RT proteins was defined solely in terms of function, but held that there was a sufficient known relationship between the structure and function of RTs to satisfy the written description requirement. In holding that the claims of the patent complied with the written description requirement despite the fact that only one RT variant was described in the patent, the court was giving weight to the existing knowledge in the particular field, the extent and context of the prior art, and the maturity of the technology at issue.

In the instant case, amended claims 20 and 22 are drawn to diabodies of CD22 that (1) have 0-3 amino acids in each of the CDRs of specified VH and VL domains substituted with another amino acid, and (2) induce apoptosis of a tumor cell expressing CD22. The application as filed discloses the sequences of two scFvs (SEQ ID NOs: 1 and 3) that form diabodies that bind CD22. The application identifies the VH (SEQ ID NO: 5 or 9) and VL (SEQ ID NO: 7 or 11) regions of both these scFvs, as well as the three CDR sequences that are present in each of the disclosed VH and VL regions.

At the priority date of the instant application, it was well known in the art that the CDRs of an antibody are primarily responsible for antigen recognition. In addition, at the priority date, much progress had already been made in antibody engineering techniques to create better antibodies. The development of methods for the cloning and expression of antibody variable region gene sequences leading to the synthesis of functional antibody fragments, together with application of methods of random and site-directed mutagenesis, greatly facilitated structure-function studies of CDRs. Many different approaches had been reported for improving the affinity of antibodies, including error-prone PCR, CDR walking, and parsimonious mutagenesis, among others (*see,* references collected in **Appendix A**). The value of these methods is further enhanced by molecular modeling, allowing the prediction of suitable amino acids for substitution

[1] The claim at issue recites: An isolated polypeptide having DNA polymerase activity and substantially reduced RNAse H activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity and wherein said nucleotide sequence is derived from an organism selected from the group consisting of retrovirus, yeast, Neurospora, Drosophila, primate or rodent.

in CDRs. The use of these techniques combined, in some instances, with powerful phage display technology (*see,* **Appendix A**, Marks *et al.*, *J. Biol. Chem.*, **267**:16007 (1992)) has permitted the routine production of variant antibodies with improved affinity well before the priority date of the instant application (*see,* **Appendix A**, Cumbers *et al.*, *Nat. Biotechnol.*, **20**:1129-1134 (2002); Schier *et al.*, *J. Mol. Biol.*, 263(4):551-67 (1996); Yang *et al.*, *J. Mol. Biol.*, **254(3)**:392-403 (1995); Deng *et al.*, *J. Biol. Chem.*, **269**:9533 (1994); Barbas *et al.*, *Proc. Natl. Acad. Sci. USA*, **91**:3809 (1994); Sharon, *Proc. Natl. Acad. Sci. USA*, **87**:4814 (1990); and Roberts, *Nature*, **328**:731 (1987)). These references clearly demonstrate the level of knowledge in the antibody engineering field and the significant maturity of this field at the priority date of this application.

Thus, at the priority date of the instant application, one of ordinary skill in the art would have recognized that Applicants were in possession of the full scope of the subject matter of claims 20 and 22. Applicants note that the Federal Circuit has explicitly stated that compliance with the written description requirement does not require either examples or actual reduction to practice (*see, Falkner v Inglis*, 448 F.3d 1357 (Fed. Cir. 2006)). Even though not required, one embodiment of each of claims 20 and 22 was explicitly described in the specification: SEQ ID NO:1 for claim 20 and SEQ ID NO:3 for claim 22. Like *Invitrogen*, where the court held that the broadly claimed RT variants were adequately described despite the fact that the patent specification disclosed only a single RT variant, Applicants respectfully submit that the subject matter of amended claims 20 and 22 is adequately described when considered in the context of the state of the art and the maturity of the technology at issue.

In view of the foregoing remarks, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

III. Rejections Under 35 U.S.C. § 102:

(a) Claims 14 and 23-27 are rejected under 35 U.S.C. § 102(a) and 35 U.S.C. § 102(e) as purportedly anticipated by Tedder (US Appl. No. 2003/0202975) (*see,* Office Action, pages 8-10, sections 14 and 16, respectively).

Claims 14 and 23-27 have been canceled without prejudice. Accordingly, these rejections under 35 U.S.C. § 102(a) and 35 U.S.C. § 102(e) are moot.

(b) Claims 14 and 23-27 are rejected under 35 U.S.C. § 102(a) and 35 U.S.C. § 102(e) as purportedly anticipated by Tuscano *et al.* (US Appl. No. 2004/0001828) *(see,* Office Action, pages 9 and 10, sections 15 and 17, respectively).

Claims 14 and 23-27 have been canceled without prejudice. Accordingly, these rejections under 35 U.S.C. § 102(a) and 35 U.S.C. § 102(e) are moot.

IV. Request for Rejoinder:

Once the composition claims are deemed allowable, Applicants respectfully request rejoinder of the withdrawn method claims that depend directly or indirectly from them.

CONCLUSION

Applicants respectfully request withdrawal of all the rejections and allowance of the claims.

Please apply the 3-month extension of time fee, the excess claims fee, and the RCE filing fee, and any other requisite charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0151US1.

If the Examiner believes that a discussion could advance the allowance of this case, she is invited to call the undersigned at the telephone number listed below.

Respectfully submitted,

Date: September 10, 2009

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APPENDIX A

Attached are the following references that are mentioned in the Remarks section of this Response:

1. Marks *et al.*, *J. Biol. Chem.*, **267**:16007-16010 (1992);
2. Cumbers *et al.*, *Nat. Biotechnol.*, **20**:1129-1134 (2002);
3. Schier *et al.*, *J. Mol. Biol.*, **263(4)**:551-567 (1996);
4. Yang *et al.*, *J. Mol. Biol.*, **254(3)**:392-403 (1995);
5. Deng *et al.*, *J. Biol. Chem.*, **269**:9533-9538 (1994);
6. Barbas *et al.*, *Proc. Natl. Acad. Sci. USA*, **91**:3809-3813 (1994);
7. Sharon, *Proc. Natl. Acad. Sci. USA*, **87**:4814-4817 (1990); and
8. Roberts, *Nature*, **328**:731-734 (1987).